Predicting which medication classes interfere with allergy skin testing

Kunal M. Shah, M.D,[1] Matthew A. Rank, M.D.,[1] Shoban A. Davé, M.D.,[2] Corrine L. Oslie, R.N.,[1] and Joseph H. Butterfield, M.D.[1]

ABSTRACT

Medications often interfere with allergy skin test interpretation. This study was performed to determine which medications interfere with allergy skin tests. We retrospectively reviewed skin-prick test results from patients who had discontinued H_1-antagonists, tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), benzodiazepines, atypical antidepressants, antipsychotics, hypnotics, sedatives, proton pump inhibitors (PPIs), and H_2-antagonists between 0 and 7 days before allergy skin testing. Ninety-seven subjects had taken second-generation H_1-antihistamines within 7 days of skin testing; all patients who had stopped 3 days before testing had positive histamine controls. Two hundred sixty-eight skin tests performed on patients taking a single medication of interest showed that patients had the following percentages of a positive histamine control: TCAs, 56.5%; SNRIs, 100%; H_2-blockers, 100%; SSRIs, 97%; PPIs, 97%; benzodiazepines, 85.7%; and atypical antidepressants/sedatives, 92.6%. The 580 patients taking multiple medications of interest showed that the odds ratio and 95% confidence intervals of a negative histamine test for patients taking TCAs were 6.33 (2.11–20.5), for H_1-blockers were 4.95 (1.78–15.1), for benzodiazepines were 5.01 (1.72–15.80), for atypical antidepressants/sedatives were 3.11 (1.09–9.61), and for H_2-blockers were 2.91 (0.97–9.37). The odds of a negative histamine test for SSRIs, SNRIs, or PPIs were not significantly increased. SSRIs, SNRIs, and PPIs are unlikely to interfere with skin testing. TCAs, H_1-blockers, benzodiazepines, quetiapine, and mirtazapine should be discontinued temporarily if clinically able. H_2-antagonists, bupropion, eszopiclone, trazodone, or zolpidem showed minimal interference with immediate hypersensitivity skin test histamine response.

(Allergy Asthma Proc 31:477–482, 2010; doi: 10.2500/aap.2010.31.3382)

Many variables involved in skin testing have been studied, including age, time of day, site being tested, extract quality, prick proximity, prick versus intradermal (ID), device, and medications.[1] Certain medications are thought to mitigate or eliminate skin reactivity to the positive histamine control rendering the allergen skin test uninterpretable. H_1-antagonists have been the best studied, and suggestions on which medications should be held and for how long are available.[2,3] H_2-antagonists are used as adjunct therapy in allergic diseases such as urticaria. H_2-antagonists have been shown to suppress histamine response in the skin to a limited degree, although the clinical relevance of this remains unknown and the recommendation is based on data mostly from ranitidine.[4] Several additional classes of medications, including antidepressants, sedatives, and proton pump inhibitors (PPIs) may interfere with allergy skin tests but have not been carefully studied.

The first antidepressant imipramine was synthesized for use as an antihistamine.[5] Chlorpromazine was found to be effective in schizophrenia.[6] Some older selective serotonin reuptake inhibitors (SSRIs) were antihistamines and the SSRI effect was discovered in 1969. The SSRI fluoxetine is related to diphenhydramine.[7] The antidepressants mirtazapine and trazodone as well as the antipsychotic quetiapine both have antihistaminic properties and are commonly prescribed for insomnia comorbid with psychiatric disorders. Benzodiazepines have been shown antagonize H_1- and H_2-receptors.[8]

Histamine is a neurotransmitter that drives wakefulness; therefore, antihistamines are included in sedatives and hypnotics sleep medications. Norepinephrine and serotonin are considered "wake-promoting" neurotransmitters. Medications for insomnia work by preventing binding to the receptors for the neurotransmitters that drive wakefulness such as histamine or promoting the ones that drive sleep by propagating the inhibition of wake promoters such as γ-aminobutyric acid.[6]

From the [1]Division of Allergic Diseases, Mayo Clinic, Rochester, Minnesota, and [2]Kaiser Permanente, Rockville, Maryland

Presented in part at the annual meeting of the American Academy of Allergy, Asthma, and Immunology, Washington, D.C., March 16, 2009; at the annual meeting of the American College of Allergy, Asthma, and Immunology, Miami, Florida, November 9, 2009; at the annual meeting of the American Academy of Allergy, Asthma, and Immunology, New Orleans, Louisiana, March 1, 2010; and was presented at the Eastern Allergy Conference, May 7, 2010

Funded by the Mayo Foundation

All study procedures and ethics for both reviews were approved by the Institutional Review Board of the Mayo Clinic

M. Rank received a research grant to his institution from Purezone, Inc.; C. Oslie, K. Shah, S. Davé, and J. Butterfield have nothing to declare pertaining to this article

Address correspondence and reprint requests to Kunal Shah, M.D., 200 First Street S.W., Mayo 15W, Rochester, MN 55905

E-mail address: shah.kunal@mayo.edu

The "Updated Practice Parameters for Allergy Diagnostic Testing" include recommendations for duration of suppression by tricyclic antidepressants (TCAs), but these are based on a study looking at the older agents desipramine, doxepin, and imipramine.[3,9] The newer and commonly used agents, such as amitriptyline have not been evaluated. Very little is known about how psychiatric medications interfere with allergy skin testing. There is a lack of data suggesting how long these medications need to be held before testing and if combinations of these medications affect the histamine control. In this study, we examined the timing of H_1-antagonist discontinuation and its effect on histamine skin tests. Next, we examined the effect from single non–H_1-antagonist medications with potential antihistaminic activity. Last, we used a multivariate model to examine patients taking multiple medications to help clarify whether specific medication classes interfere with histamine skin tests. The overall goal of the study was to facilitate timely testing and avoid unnecessary medication discontinuation.

METHODS

A retrospective medical record review from March 2006 to February 2008 was performed on patients undergoing allergy skin tests who had discontinued second-generation antihistamine therapy within 0–7 days of skin testing. Subsequently, medical records were reviewed from January 2008 to March 2009 on patients undergoing allergy skin tests who had taken second-generation H_1-antagonists (cetirizine, fexofenadine, and loratadine/desloratadine), TCAs (amitriptyline and nortriptyline), SSRIs (citalopram, escitalopram, fluoxetine, paroxetine, and sertraline), selective norepinephrine reuptake inhibitors (SNRIs; venlafaxine and duloxetine), benzodiazepines (clonazepam, diazepam, lorazapam, and midazolam), atypical antidepressants/sedatives (bupropion, eszopiclone, mirtazapine, trazodone, quetiapine, and zolpidem), PPIs (esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole), and H_2-antagonists (famotidine, ranitidine, and cimetidine within 7 days of allergy skin testing). Before skin testing our nurses recorded current and recent medication use on the skin test results. Skin tests were placed on the volar surface of the forearm using 6 mg/mL of histamine prick or ID (0.1 mg/mL) as the positive control. The response to histamine was considered positive if the skin test response was measured as greater than a 3 × 3-mm wheal with flare. All study procedures and ethics for both reviews were approved by the Institutional Review Board of the Mayo Clinic.

Data Analysis

Univariate comparisons between groups were performed using two-sample *t*-tests for continuous variables and chi-square tests for nominal variables. The effects of multiple medication classes, days discontinued before testing, and total number of medications were determined using multivariate logistic regression and were reported as the odds ratio (OR) of a negative histamine skin test with 95% confidence intervals. Statistical analysis was performed using JMP statistic software, Version 8 (SAS Institute, Inc., Cary, NC). Values of $p < 0.05$ were considered statistically significant.

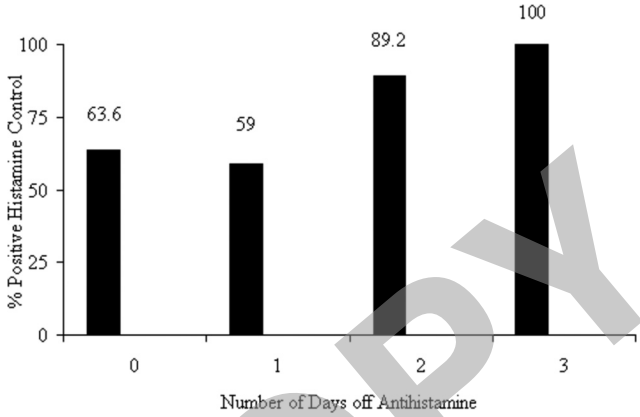

Figure 1. *Percent of positive histamine responses in patients taking cetirizine, fexofenadine, or loratadine/desloratadine from 0 to 3 days before skin testing.*

RESULTS

H_1-Antihistamines

We initially examined the timing of discontinuing second-generation H_1-antagonists on histamine controls in 97 patients undergoing allergy skin testing. We identified 34 patients recently treated with fexofenadine, 35 patients treated with cetirizine, and 28 patients who were treated with either loratadine or desloratadine in the previous 7 days. In the group who had taken their second-generation H_1-antagonists within 24 hours of testing, all of the patients treated with fexofenadine (100%) and most patients treated with loratadine/desloratadine (75%) had positive histamine control responses, and none of the patients who had taken cetirizine had a positive histamine control test. In the patients who discontinued second-generation H_1-antagonists 24–48 hours before testing, histamine controls were positive for 88% taking fexofenadine, 79% taking loratadine/desloratadine, and 63% taking cetirizine. When all second-generation H_1-antagonists were considered together, the patients who had discontinued at 1 and 2 days before testing had 59 and 89% positive histamines, respectively (Fig. 1). All patients that discontinued H_1-antagonists 3 days before testing had positive histamine control responses. In this initial retrospective analysis, 23% of the patients with negative histamine controls were on H_2-antagonists or SSRIs within 1 day of testing. This prompted us

to question the role of other drugs known to have antihistaminic properties on histamine skin test responses.

Other Agents with Antihistaminic Properties

We then reviewed skin tests from patients reporting use of TCAs, SSRIs, SNRIs, PPIs, benzodiazepines, atypical antidepressants/sedatives, and H_1- and H_2-antagonists. We initially considered the histamine skin-prick responses in patients taking agents from a single medication class and later looked at the effects of multiple medications and days of discontinuation.

The results from 268 skin tests from patients on a single medication of interest showed that TCAs, benzodiazepines, and atypical antidepressants interfered with histamine controls. Patients on TCAs had a 56.5% chance of having a positive histamine control. Patients on benzodiazepines had an 85.7% chance of having a positive histamine control. Patients on atypical antidepressants/sedatives had a 92.6% chance of having a positive histamine control. Patients on H_2-blockers, SSRIs, SNRIs, and had a 97–100% chance of having a positive histamine control. Results are summarized in Table 1.

Next, we looked at 580 charts of patients on multiple medications. Fifty percent of these patients were taking medications from two or more of the medication classes studied. Forty percent were taking two medications, 9.1% were taking three medications, 0.6% were taking four medications, and one patient was taking medications from five of the medication classes studied. The median number of medications was two with a range of one to five. The total number of medications did not increase the odds of a negative histamine skin test (OR = 0.82, 0.32–1.87).

Using the multivariate model to account for effects of multiple medications, the odds of a negative histamine test for patients taking TCAs was 6.33 (2.11–20.5), for H_1-blockers was 4.95 (1.78–15.1), for benzodiazepines was 5.01 (1.72–15.80), for atypical antidepressants/sedatives was 3.11 (1.09–9.61), and for H_2-blockers was 2.91 (0.97–9.37). The odds of a negative histamine test for SSRIs, SNRIs, or PPIs were not significantly increased (summarized in Table 2).

Next, we performed a separate univariate analysis of patients on atypical antidepressants, which showed the number of negative histamine responses were more significant in those taking quetiapine and mirtazapine. All of the four patients on mirtazapine had negative histamine controls ($p < 0.001$). Quetiapine suppressed histamine in 73% of 11 patients ($p < 0.001$). The patients on bupropion, eszopiclone, trazodone, or zolpidem had positives histamine responses in 75–79% of tests (Table 3).

We evaluated the timing of medication discontinuation using the multiple medication statistical model. As expected, the odds of a negative skin test for all of medications that we considered in this study decreased for each day off of medication by 0.67 (0.50–0.87). Eighty-nine percent had discontinued their medications <48 hours before skin testing, with more than one-half having taken the medications within 24 hours of testing. Six percent had stopped taking medications 72 hours before testing and 1.6% of patient's last reported dose was 96 hours before testing. Approximately 3% of skin tests were from patients having taken their medications between 5 and 7 days before testing.

Table 1 **Single medication data**

Drug Class	*n*	% Positive Histamine
TCAs	23	56.5
Amitriptyline		
Nortriptyline		
Benzodiazepines	7	85.7
Clonazepam		
Diazepam		
Lorazepam		
Midazolam		
Atypical antidepressants/ sedatives	54	92.6
Bupropion		
Eszopiclone		
Mirtazapine		
Trazodone		
Quetiapine		
Zolpidem		
H_2-blockers	19	100
Famotidine		
Ranitidine		
Cimetidine		
SSRI	77	97
Citalopram		
Escitalopram		
Fluoxetine		
Paroxetine		
Sertraline		
SNRI	26	100
Venlafaxine		
Duloxetine		
PPI	62	97
Esomeprazole		
Lansoprazole		
Omeprazole		
Pantoprazole		
Rabeprazole		

PPIs = proton pump inhibitors; SNRIs = selective norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors; TCA = tricyclic antidepressants.

Table 2 **Odds of negative histamine control by medication class**

Medication	Odds Ratio	95% Confidence Interval
TCAs	6.33	(2.11–20.5)
Amitriptyline		
Nortriptyline		
Benzodiazepines	5.01	(1.72–15.80)
Clonazepam		
Diazepam		
Lorazepam		
Midazolam		
H_1-blockers (second generation)	4.95	(1.78–15.1)
Cetirizine		
Fexofenadine		
Loratadine		
Atypical antidepressants/ sedatives	3.11	(1.09–9.61)
Bupropion		
Eszopiclone		
Mirtazapine		
Trazodone		
Quetiapine		
Zolpidem		
H_2-blockers	2.91	(0.97–9.37)
Famotidine		
Ranitidine		
Cimetidine		
PPIs	2.02	(0.78–5.73)
Esomeprazole		
Lansoprazole		
Omeprazole		
Pantoprazole		
Rabeprazole		
SSRIs	1.37	(0.51–3.96)
Citalopram		
Escitalopram		
Fluoxetine		
Paroxetine		
Sertraline		
SNRIs	1.15	(0.36–3.85)
Venlafaxine		
Duloxetine		

PPIs = proton pump inhibitors; SNRIs = selective norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors; TCA = tricyclic antidepressants.

Finally, to address concerns that the medications may result in a blunted prick response, we noted the average wheal area of the histamine skin test for all of the study subjects. Our nurses measured the wheal length and width with a millimeter ruler. These values were multiplied to establish a relative wheal size. The average relative wheal size for all prick tests was 37.5. The average was 33 for the TCAs, 36 for SSRIs, 39 for SNRIs, 36 for H_2-antagonists, 42 for benzodiazepines, 38 for PPIs, 37 for atypical antidepressants, and 38 for H_1-antagonists.

Table 3 **Negative histamine controls in patients on atypical antidepressant/sedatives**

Drug	*n*	% (−) Histamine	*p* Value
Mirtazapine	4	100	0.0003
Quetiapine	11	72.7	0.0001
Eszopiclone	16	25	0.86
Bupropion	27	22.2	0.91
Zolpidem	73	21.9	0.80
Trazodone	61	21.3	0.73

DISCUSSION

This study confirms that nonsedating H_1-antagonists and TCAs inhibit histamine skin tests and discontinuation within 3 days for the former and 7 days for the latter medication class is sufficient for obtaining an appropriate histamine control for skin testing interpretation. Additionally, our findings suggest that patients on benzodiazepines, mirtazapine, and quetiapine should be temporarily discontinued before skin testing if clinically able because these agents showed suppression of histamine skin tests. Most patients on bupropion, eszopiclone, trazodone, and zolpidem had positive histamine skin tests. Patients on H_2-antagonists alone all had positive histamine skin tests; however, if they were also on other potentially antihistaminic medications their odds of a negative histamine control increased, possibly because of an additive effect. Patients on PPIs, SSRIs, and SNRIs did not suppress histamine skin tests, suggesting that patients should be allowed to continue these medications before skin testing.

Our data allowed for predictions of histamine skin test suppression based on the timing of medication discontinuation. The "Updated Practice Parameters for Allergy Diagnostic Testing" recommend discontinuation of most first- and second-generation H_1-antagonists 2–3 days before skin testing. They recommend waiting longer for cetirizine, loratadine, hydroxyzine, clemastine, and cyproheptadine.[3] Findings from our study suggest that 3 days of discontinuation of second-generation H_1-antagonists was sufficient to develop a positive histamine control.

The recommendation of 24 hours of discontinuation for H_2-antagonists is derived primarily from ranitidine data. Many of the previous studies were performed using ID injection of the H_2-antagonist and then skin

testing over the injected skin.[3] The effects of clemastine with ranitidine showed some inhibition of allergen-induced wheal and flare, but ranitidine alone did not.[10] Miller *et al.* showed that 150 mg of ranitidine twice a day for 7 days suppressed the size of the histamine wheal by 22% compared with placebo. They recommended continuation of H_2-antagonists before testing or holding only one dose.[4] A more recent double-blind placebo-controlled study found that 5 days of 150 mg/day of ranitidine resulted in reduction of wheal area and itching from histamine, codeine, and allergen extracts.[11] Our results, based on data from current clinical practice, are consistent with these previous studies in that H_2-antagonists may be important in suppressing histamine skin tests, but only if taken with other potentially antihistaminic medications.

Authors of the "Updated Practice Parameters for Allergy Diagnostic Testing" recommend TCAs be discontinued 6 days before skin testing based studies using the older TCAs (desipramine, doxepin, and imipramine).[3] A previous study of TCAs found that single 25-mg doses of doxepin and desipramine inhibited the histamine-induced wheal and flares for 2 and 6 days, respectively.[5] In our study of 23 patients taking amitriptyline or nortriptyline between 0 and 7 days before skin testing, 56.5% had positive histamine controls. The patients who were on a TCA and other medications had the most significant odds of a negative histamine control.

The atypical antidepressant medications considered in our study suggest these medications may interfere with allergy skin testing. γ-Aminobutyric acid-A receptor modulators such as barbiturates, zolpidem, zaleplon, and eszopiclone theoretically should not affect histamine skin tests. A recent study showed inhibition of the histamine wheal in patients taking alprazolam daily.[8] We evaluated seven patients taking benzodiazepines alone; most had positive histamine skin tests. However, we found that patients taking benzodiazepines along with other potential antihistaminic agents had a 5.01 OR for having a negative histamine control. As expected, mirtazapine (α2/5HT2 antagonist) and quetiapine were statistically significant inhibitors of histamine controls. Mirtazapine and quetiapine have higher potency H_1-antagonism and weaker effects on serotonin and norepinephrine transporter.[6] Although older SSRIs or SNRIs were related to antihistamines, we found that current SSRIs and SNRIs are unlikely to interfere with allergy skin testing.

Study Limitations

Because of the retrospective study design, we relied on patient recollection of their medications and the timing of medication discontinuation. Patients can over- or underreport use of medications, although re-

Table 4 **Recommendations on drug discontinuation before skin testing**

Drug Class	Recommended Discontinuation (day)
H_1-blockers (second generation)	3–5
Cetirizine	
Fexofenadine	
Loratadine	
TCAs*	5–7
Amitriptyline	
Nortriptyline	
Benzodiazepines*	5–7
Clonazepam	
Diazepam	
Lorazepam	
Midazolam	
Atypical antidepressants/sedatives*	
Mirtazapine*	5–7
Quetiapine*	
Bupropion*	0–3
Eszopiclone*	
Trazodone*	
Zolpidem*	
H_2-blockers#	0–2
Famotidine	
Ranitidine	
Cimetidine	
SSRIs	No need to discontinue
Citalopram	
Escitalopram	
Fluoxetine	
Paroxetine	
Sertraline	
SNRIs	No need to discontinue
Venlafaxine	
Duloxetine	
PPIs	No need to discontinue
Esomeprazole	
Lansoprazole	
Omeprazole	
Pantoprazole	
Rabeprazole	

**If clinically able.*
#Especially if combined with another potentially antihistaminic medications.
PPIs = proton pump inhibitors; SNRIs = selective norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors; TCA = tricyclic antidepressants.

call bias was limited by asking patients their current medication use just before skin testing. Our data included ID histamine tests, which may behave differently from prick tests. Approximately 8% of the tests included both prick and IDs and the results of both positively correlated in 73% of tests. Skin test responses were ascertained by eight allergy clinic nurses skilled with skin test response measurements. Nonetheless, the possibility of measurement bias can not be completely excluded.

There is a theoretical concern that the studied medications may partially suppress histamine skin tests and potentially affect the results of other antigen results. Our data of average histamine area between different medication classes showed no significant variability. It is possible that other mast cell mediators besides histamine may be important in determining the skin test response to antigens,[12] which could be addressed in a prospective study using controls with known positive antigen tests. Finally, for some medications, particularly atypical antidepressants and benzodiazepines, we accumulated a small number of patients, leaving less certainty about the effects of these medications on histamine skin tests.

Clinical Implications

Allergists must advise their patients which medications to hold before allergy skin testing and how long they need to be held. Often patients do not want to stop their H_1- and H_2-antagonists or PPIs for an extended time for fear of recurrence of their daily symptoms. Many are also dependent on sedatives for sleep and are unwilling to hold these medications. Antidepressants and antipsychotics should not be abruptly discontinued without assistance from the prescribing provider. SSRIs are the most widely prescribed antidepressants in the United States.[13] Presently, TCAs also have indications for attention deficit hyperactivity disorder and chronic pain but are frequently used off label for fibromyalgia, migraines, anxiety disorders, smoking cessation, irritable bowel syndrome, cough reflex syndrome, and chronic urticaria. Ideally, the allergist should discontinue medications for the minimal time necessary to produce accurate skin test results and, more importantly, avoid cessation of drugs that do not affect the testing. The data from this study can help inform these decisions.

SSRIs, SNRIs, and PPIs are unlikely to interfere with allergy skin testing and should not be discontinued before allergy skin testing. TCAs, H_1-antagonists, benzodiazepines, quetiapine, and mirtazapine should be discontinued briefly before skin testing if clinically able (Table 4). If these medications are discontinued for the recommended time before skin testing, it is very unlikely they will interfere with allergen skin test interpretation based on our experience with histamine skin tests responses. H_2-antagonists alone are unlikely to interfere with skin testing, but if taken with other agents may need to be held for 24–48 hours. Additional studies with prospective designs are needed to confirm our findings.

ACKNOWLEDGMENTS

The authors thank the nurses in our allergy laboratory (L15) for their assistance in collecting the data, Jennifer Krogman for helping with the data entry, and Arun Rote for data extraction. They also appreciate the help from the Center for Translational Science Activities at Mayo Clinic in our statistical analysis.

REFERENCES

1. Nelson HS. Variables in allergy skin testing. Allergy Proc 15: 265–268, 1994.
2. Demoly P, Bousquet J, and Romano A (Ed). In vivo Methods for Study of Allergy: Skin Tests, Techniques and Interpretation, Chapter 71, 7th ed. New York: Mosby, 1271–1272, 2008.
3. Bernstein IL, Li JT, Bernstein DI, et al. Allergy diagnostic testing: An updated practice parameter. Ann Allergy Asthma Immunol 100:S1–S148, 2008.
4. Miller J, and Nelson HS. Suppression of immediate skin tests by ranitidine. J Allergy Clin Immunol 84:895–899, 1989.
5. Rao KS, Menon PK, Hilman BC, et al. Duration of the suppressive effect of tricyclic antidepressants on histamine-induced wheal-and-flare reactions in human skin. J Allergy Clin Immunol 82:752–757, 1988.
6. Stahl SM. Selective histamine H1 antagonism: Novel hypnotic and pharmacologic actions challenge classical notions of antihistamines. CNS Spectr 13:1027–1038, 2008.
7. Hellbom E. Chlorpheniramine, selective serotonin-reuptake inhibitors (SSRIs) and over-the-counter (OTC) treatment. Med Hypotheses 66:689–690, 2006.
8. Duenas-Laita A, Ruiz-Munoz P, Armentia A, et al. Successful treatment of chronic drug-resistant urticaria with alprazolam. J Allergy Clin Immunol 123:504–505, 2009.
9. Rao KS, Menon PK, Hilman BC, et al. Duration of the suppressive effect of tricyclic antidepressants on histamine-induced wheal-and-flare reactions in human skin. J Allergy Clin Immunol 82:752–757, 1988.
10. Meyrick Thomas RH, Browne PD, and Kriby JD. The effect of ranitidine, alone and in combination with clemastine, on allergen-induced cutaneous wheal and flare reactions in human skin. J Allergy Clin Immunol 76:864–869, 1985.
11. Kupczyk M, Kupryś I, Bocheńska-Marciniak M, et al. Ranitidine (150 mg daily) inhibits wheal, flare, and itching reactions in skin-prick tests. Allergy Asthma Proc 28:711–715, 2007.
12. Weller K, and Maurer M. Desloratadine inhibits human skin mast cell activation and histamine release. J Invest Dermatol 129:2723–2726, 2009.
13. Stahl SM. Basic psychopharmacology of antidepressants, part 1: Antidepressants have seven distinct mechanisms of action. J Clin Psychiatry 59(suppl 40):5–14, 1998. □